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Letter to the Editor

An Additional Monogenic Disorder That Masquerades as Multiple Sclerosis

To the Editor:

In their comprehensive differential diagnosis of monogenic diseases that can mimic multiple sclerosis, Natowicz and Bejjani [1995] did not include a newly recognized monogenic disorder known under the acronym of CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) [Tournier-Lasserve et al., 1993]; this disorder can mimic MS clinically and radiologically to a remarkable extent.

The underlying histopathological lesion of CADASIL is a non-atherosclerotic, non-amyloid arteriopathy affecting mainly the penetrating medullary arteries to the subcortical white matter and basal ganglia. Electron microscopy shows an abnormal deposit of granular osmiophilic material in the arterial wall [Baudrimont et al., 1993; Ruchoux et al., 1994]. These arterial changes are observed in various tissues even though clinical manifestations seem to be restricted to the central nervous system [Ruchoux et al., 1995]. The CADASIL gene was mapped recently to chromosome 19 [Tournier-Lasserve et al., 1993] and gene identification is ongoing.

CADASIL often presents in adults (mean age at onset = 45 ± 10 years) with recurrent multifocal neurological deficits associated with diffuse cerebral white matter abnormalities (Fig. 1) [Chabriat et al., 1995]. These recurrent episodes are either transient or partially regressive and are highly suggestive of small subcortical infarcts. In more than 30% of cases the patients also suffer from migraine with aura. Personality changes and mood disorders (depression or mania) as well as slowly progressive subcortical dementia are the other presentations of CADASIL. Acute confusional episodes and seizures are reported less commonly. All of these clinical manifestations are constantly associated with MRI white matter abnormalities which may precede clinical symptoms by several years [Tournier-Lasserve et al., 1993].

The absence of clinical manifestations other than central nervous system involvement, the recurrence of multifocal neurological deficits with relatively young age-of-onset, slow progression to spastic tetraparesis, urinary incontinence, pseudobulbar palsy, subcortical dementia, and periventricular white matter abnormalities on MRI that initially are patchy and multifocal, and later become confluent, may simulate MS. In addition, extensive vascular investigations are negative and oligoclonal IgG fractions in spinal fluid have been reported in a few cases [Chabriat et al., 1995]. Incorrect initial diagnosis of MS was made in several of the CADASIL patients that were referred to us and led to inappropriate treatment.

Key points differentiating CADASIL from MS are absence of optic neuritis; absence of spinal cord involve-

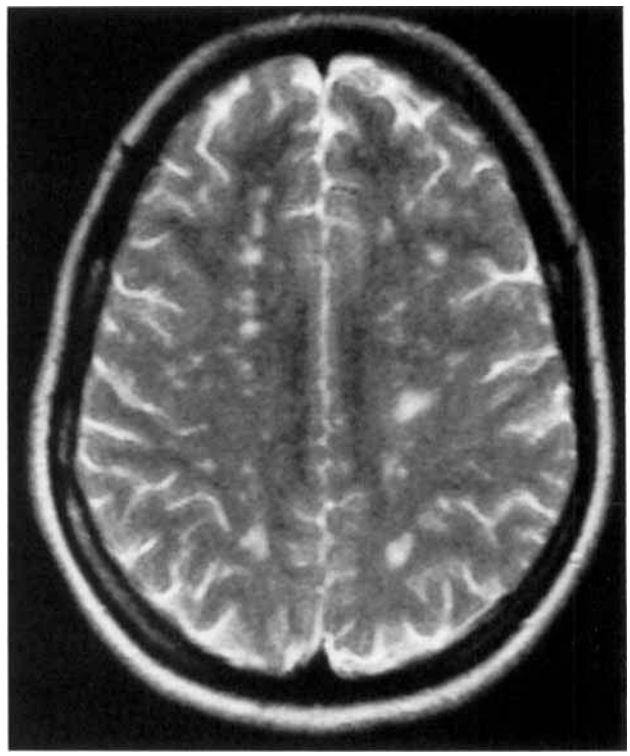

Fig. 1. Cranial MRI of a 39-year-old-woman showing extensive white matter hyperintensities on T2WI. This woman has had at the age of 33 one transient episode of blurred vision of the left eye lasting 24 hours. Six months later she had a transient episode of dysphasia lasting 2 hours. At the age of 34 she has had a right hemiparesis lasting 1 month. She suffers migraine with aura since the age of 36. Immunologic, hematologic and cardio-vascular investigations were normal. CSF examination showed oligoclonal IgG fraction and 5 cells/mm^3.

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ment; presence of basal ganglia MRI lesions; and a positive family history of dominantly inherited stroke, vascular dementia, and migraine with aura and associated diffuse white matter abnormalities. It should be stressed that the familial nature of this disorder is very often overlooked because of its variable and nonspecific clinical presentation and its sometimes late age-of-onset (range from 25 to 60 years).

The evaluation of patients with clinical and MRI findings suggestive of CADASIL should include a skin biopsy for ultrastructural study of the cutaneous arteries which may show the same arterial wall lesions as in brain small arteries, and genetic linkage analysis to the CADASIL locus on chromosome 19 using closely linked markers in several informative members of the family. Accurate diagnosis is crucial for the understanding of its clinical presentation, natural history, and prognosis, for the correct estimation of its prevalence, for the identification of its underlying genetic lesion, and for appropriate genetic counseling and organisation of future therapeutic trials.

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